Cancer Recurrence After Surgery

A Role for Regional Anesthesia?

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Most cancer surgery is performed with curative intent. Despite complete resection to microscopically negative margins, however, cancer deaths subsequent to surgery remain common because of metastatic disease. Investigators have developed and continue to refine a variety of adjuvant and neoadjuvant systemic treatments for cancer patients with the intent of obliterating disseminated disease before it becomes a life-threatening metastatic burden. The importance of these systemic treatments underscores the statistical likelihood that many patients harbor micrometastatic disease at the time of clinical presentation. These tumor cells increase in volume because of seeding at the time of resection or because of an increased growth rate after surgery. In addition, the variety of existing cytotoxic agents and targeted systemic treatments that are currently in use and in development attest to the biologic complexity of metastatic pathways.

Cancer dissemination requires release ("shedding") of metastatic cells from a primary tumor, cell migration (local, lymphatic, intravascular) to a metastatic site, adherence and/or endothelial migration, angiogenesis, and, most importantly, evasion of host immune surveillance. At each step, there are a myriad of cellular and molecular regulatory processes that may be susceptible to therapeutic intervention. Adjuvant cytotoxic systemic therapy is generally delayed weeks after surgery to facilitate wound healing before the administration of medications, which could lead to immune suppression and increase the risk of postoperative infection. However, there are many studies to show that cellular and molecular events that are critical to the metastatic process may be significantly influenced during and immediately after surgery. Peach et al[1] recently reported that the presence of circulating tumor cells in the blood 24 hours after colon surgery is a negative prognosticator for overall survival. This suggests the perioperative period as a possible window of therapeutic opportunity for eradication of micrometastatic cancer. In addition, events that are a critical part of recovery from major surgery including inflammation, wound healing, and the neuroendocrine (stress) response to major injury may also be involved in determining the likelihood of cancer recurrence after surgery.[2] These observations all suggest that there may be an opportunity to interrupt the metastatic process before initiation of traditional systemic therapy.

Although 95% to 97% of women diagnosed with breast cancer have no detectable clinical evidence of distant metastatic disease at the time of presentation, breast cancer remains the second leading cause of cancer death among American women. Women with nodal involvement at the time of presentation have an 83% 5-year survival (http://seer.cancer.gov/statfacts/html/breast.html#survival) with death resulting from the development of distant metastasis. This underscores the resilience of circulating tumor cells that endure despite surgical and systemic therapies. Breast cancer surgery is less physiologically and metabolically disruptive than surgery for intra-abdominal and intrathoracic malignancies. As a consequence, breast cancer may be an ideal target for investigation of interventions that are designed to minimize perioperative perturbations that have been linked to cancer recurrence and metastasis. In this issue of *Regional Anesthesia and Pain Medicine*, Deegan et al[3] provide an example of how two disparate anesthetic techniques, both with generally accepted clinical response profiles, can manifest significantly different effects on intermediate outcomes that are experimentally associated with cancer recurrence. Most notably, their study addresses the previously demonstrated concepts that the minimization of pain[4] and opiate consumption[5] may decrease the risk of cancer recurrence. In addition, the authors examine the possibility that soluble mediators of the neuroendocrine and/or tissue injury response, both of which are potentially associated with the metastatic process, may be manipulated by anesthetic technique. The authors compared propofol anesthesia combined with a continuous paravertebral block to sevoflurane anesthesia combined with systemic opiate analgesia. The former technique was chosen presumably because of animal evidence that propofol, in comparison to other general anesthetics, does not inhibit natural killer (NK) cell antitumor activity and is associated with fewer experimental lung tumor metastases. In addition, paravertebral

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blocks have been retrospectively associated with a decreased incidence of breast cancer recurrence in humans.[6] In contrast, both inhalational anesthetics[7] and opiates[5] have been associated with impaired immunity and increased tumor recurrence in animals and with impaired immunity in humans.[8]

The establishment and/or progression of metastatic disease depends on a complex balance of multiple molecular and proteomic activities. Many of these pathways are perturbed by anesthesia, surgery, and the physiologic response to surgery. It is therefore reasonable to suggest that manipulation of one or several of these factors during and after surgery could affect the cancer recurrence rate. The experimental design of the study by Deegan et al is based on the premise that micrometastases (either preexisting or "seeded" during surgical manipulation of the primary tumor) can permanently escape immune surveillance in the early postoperative period and lead to metastatic disease over time. The mechanism of this evasion is likely multifactorial and may be due to transient suppression of cellular immunity and/or to stimulation of tumor growth by protumorigenic factors. There is a considerable body of research to support this concept, although most of it has been conducted in animals using experimental metastatic models. Retrospective data from human studies, however, have revealed that the use of regional anesthetics may favorably affect intermediate end points such as NK cell antitumor activity and release of soluble mediators that are associated with tumor growth thereby reducing cancer recurrence rates.[6,9]

Deegan et al recognize that multiple complex biological phenomena are associated with cancer progression. They acknowledge this by measuring a wide variety of inflammatory mediators and tissue injury response mediators. Their results offer some hope for an effective, easily implemented intervention (regional anesthesia) to reduce cancer recurrence after breast cancer surgery. The results also raise several important questions: Which of the many perioperative responses that may be associated with cancer recurrence are of primary importance, and when in the perioperative period would these responses be most effectively targeted? Would NK cell activity be most important for eliminating cancer cells released into the circulation during surgery, whereas would other factors, such as matrix metalloproteinases, be more important for growth of preexisting micrometastases because of the effects on intercellular adherence or angiogenesis? How important are interindividual or patient-specific factors? The authors studied a wide age range (18–85 years), yet recent data suggest that old age may be an important determinant for the relevance of perioperative events.[10] Given that the stress response to surgery persists over time, is there an optimal time window and duration for effective intervention? Finally, how important are interactions between anesthetic manipulations and surgery? Fentanyl alone, for example, may stimulate NK activity,[11] whereas fentanyl plus surgery suppresses NK activity.[8] Similarly, general anesthesia alone does not suppress NK activity,[12] whereas general anesthesia plus surgery is associated with suppressed NK activity.

As surgical treatments for cancer continue to evolve, it will be important to identify key cellular mechanisms by which perioperative management, including anesthetic management, may affect cancer recurrence. For example, data showing that anesthetic technique may affect cancer recurrence after open prostatectomy[9] will have to be reexamined in an era when laparoscopic techniques minimize physiologic responses to surgery.[13] What will happen if new neoadjuvant therapies markedly reduce minimal residual disease? With less potential for surgical seeding, will there be a role for regional anesthesia and blunting of the protumorigenic immune response? Results from ongoing multi-institutional prospective trials, including a study of anesthetic technique for breast cancer patients,[14] will be important to find the answers to these questions. Ultimately, it may not be possible to define a permanent role for a particular anesthetic technique in cancer surgery. However, studies such as the one by Deegan et al are valuable not only because they examine the possibility that anesthetic management affects cancer outcomes but also because of what we learn about the metastatic process and how to interrupt it.

REFERENCES

1. Peach G, Kim C, Zacharakis E, Purkayastha S, Ziprin P. Prognostic significance of circulating tumour cells following surgical resection of colorectal cancers: a systematic review. *Br J Cancer*. 2010;102: 1327–1334.
2. Gottschalk ASS, Ford J, Durieux ME, Tiouririne M. The role of the perioperative period in recurrence after cancer surgery. *Anesth Analg*. 2010;110:1636–1643.
3. Deegan CA, Murray D, Doran P, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. *Reg Anesth Pain Med*. 2010;35:490–495.
4. Page GG, Blakely W, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor promoting effects of surgery in rats. *Pain*. 2001;90:191–199.
5. Shavit Y, Ben-Eliyahu S, Zeidel A, Beilin B. Effects of fentanyl on natural killer cell activity and on resistance to tumour metastases in rats. Dose and time study. *Neuroimmunomodulation*. 2004;11:255–260.
6. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology*. 2006;105:660–664.
7. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastases by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. *Anesth Analg*. 2003;97:1331–1339.
8. Beilin BSY, Hart J, Mordashov B, Cohn S, Notti I, Bessler H. Effects of anesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. *Anesth Analg*. 1996;82:492–497.
9. Biki BME, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology*. 2008;109:180–187.
10. Gottschalk A, Ford JG, Regelin CC, et al. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. *Anesthesiology*. 2010;113:27–34.
11. Yeager MPPM, DeLeo JA, Arruda JL, Hildebrandt L, Howell AL. Intravenous fentanyl increases natural killer cell cytotoxicity and circulating $CD16^{+}$ lymphocytes in humans. *Anesth Analg*. 2002; 94:94–99.
12. Procopio MA, Rassias AJ, DeLeo JA, Pahl J, Hildebrandt L, Yeager MP. The in vivo effects of general and epidural anesthesia on human immune function. *Anesth Analg*. 2001;93:460–465.
13. Buunan MGM, Veldkamp R, Meijer DW, Bonjer HJ, Bouvy ND. Stress response to laparoscopic surgery: a review. *Surg Endosc*. 2004;18:1022–1028.
14. Sessler DIB-ES, Mascha EJ, Parat MO, Buggy DJ. Can regional anesthesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. *Contemp Clin Trials*. 2008;29:517–526.

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